

PHARMACOTHERAPY

The Efficacy and Tolerability of Inhaled Montelukast Plus Inhaled Mometasone Compared with Mometasone Alone in Patients with Chronic Asthma

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Background. The efficacy of oral montelukast in chronic asthma is well established. Montelukast is also an effective adjunctive therapy to inhaled corticosteroids (ICS) in asthma uncontrolled on ICS alone. Inhaled montelukast was recently shown to provide significant bronchodilation compared with placebo in patients with chronic asthma. The purpose of this study was to evaluate the efficacy of inhaled montelukast added to inhaled mometasone. **Methods.** This was an 8-week, multicenter, randomized, double-blind, placebo-controlled study comparing once-daily inhaled montelukast 1 mg plus inhaled mometasone 220 µg (delivered by separate dry powder inhalers) with placebo plus inhaled mometasone 220 µg. Men and women aged 15–85 years with chronic asthma, forced expiratory volume in 1 second (FEV₁) 50–80% of the predicted value, and β-agonist reversibility ≥12% were eligible. Patients were required to meet a minimum symptom threshold while receiving open-label inhaled mometasone during a 3-week prestudy/run-in period. Patients received blinded (montelukast vs. placebo) treatment for 2 weeks, entered a 1-week washout period, then crossed over to the other treatment for 2 weeks. The primary endpoint was the average change from baseline in FEV₁ over the 2-week treatment period. Secondary endpoints included daytime and nighttime symptom scores. Other endpoints included short-acting β-agonist (SABA) use, asthma exacerbations, asthma control, peak expiratory flow (PEF), and blood eosinophil count. **Results.** A total of 134 patients were randomized. For the primary endpoint, change from baseline in FEV₁, inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone (least squares mean 0.22 L vs. 0.17 L; $p = .033$ [two-sided at $\alpha = 0.05$]). Inhaled montelukast plus inhaled mometasone was also significantly more effective than placebo plus inhaled mometasone in improving daytime asthma symptom scores ($p = .005$) and nighttime asthma symptom scores ($p = .015$), increasing the percentage of days with asthma control ($p = .004$), decreasing the percentage of days with asthma exacerbations ($p \leq .001$), and decreasing the blood eosinophil count ($p = .013$). Differences were not significant on AM or PM PEF or SABA use, although the latter approached significance ($p = .073$). Both treatments were well tolerated. **Conclusion.** Inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus inhaled mometasone in improving FEV₁, symptoms, asthma control, and blood eosinophil count.

Keywords asthma, control, FEV₁, inhaled corticosteroids, mometasone, montelukast

INTRODUCTION

The efficacy and tolerability of oral montelukast in chronic asthma has been well established (1). In addition to its role as asthma monotherapy, montelukast added to inhaled corticosteroids (ICS) is more effective than ICS alone in improving lung function, asthma symptoms, peak expiratory flow (PEF), asthma exacerbations, asthma attacks, short-acting β-agonist (SABA) use (2, 3), and steroid tapering (4–6). These findings have been confirmed in subsequent meta-analyses of montelukast (7) and of antileukotrienes in general (8, 9). As such, montelukast and other antileukotrienes are one of the recommended adjunctive therapies to ICS in patients with

asthma whose symptoms are not adequately controlled on ICS alone (10).

A recent phase I dose-exploration study evaluating the efficacy of a single inhalation of montelukast in chronic asthma demonstrated significant bronchodilation that occurred within 20 minutes of administration and persisted for the full 24-hour observation period compared with placebo (11). The purpose of this proof-of-concept phase IIa study was to compare once-daily inhaled montelukast plus once-daily inhaled mometasone versus placebo plus inhaled mometasone in patients with chronic asthma.

METHODS

Patients

Nonsmoking men and women aged 15–85 years with a 1-year history consistent with chronic asthma, forced expiratory volume in 1 second (FEV₁) 50–80% predicted, and 12% reversibility after SABA administration were

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eligible. Patients were required to have been treated with SABA within 4 weeks of screening (which could have been in addition to regular treatment with ICS or ICS/long-acting β -agonist (LABA)).

Pertinent exclusion criteria included emergency room visit for asthma within 4 weeks, hospitalization for asthma within 2 months, or respiratory tract infection within 4 weeks (or within 2 months if antibiotics were required), and body mass index <19 and >35 kg/m². Excluded asthma medications included inhaled long- or short-acting anticholinergic agents within 2 weeks; oral, intravenous, intramuscular, or rectal corticosteroids within 4 weeks; xanthine derivatives or combinations within 2 weeks; leukotriene receptor antagonists within 3 days; leukotriene synthesis inhibitors within 2 weeks; or omalizumab within 4 weeks. Immunotherapy was permitted if started ≥ 6 months before screening and if the dose remained stable throughout the study. Patients using ICS and ICS/LABA combinations were eligible for enrollment.

Study Design

This trial (Merck Protocol 386, clinicaltrials.gov identifier: NCT00666679) was a randomized, double-blind, placebo-controlled crossover study conducted at 25 international sites from May 2008 to February 2009. All patients and/or legal guardians provided written informed consent prior to participation. This study was conducted in accordance with the standards of Good Clinical Practice and consistent with the standards established by the Declaration of Helsinki. The protocol was approved by the appropriate institutional review boards.

Eligible patients were switched from existing asthma medication to open-label inhaled mometasone furoate 220 μ g once daily delivered by dry powder inhaler (DPI, AsmanexTM TwisthalerTM) for 2 weeks (Period I, prestudy), after which patients entered a 1-week run-in period with open-label inhaled mometasone plus single-blind inhaled placebo using a second DPI, the

HandiHalerTM (Period II, run-in) (Figure 1). During this period, eligible patients were required to have a total overall daytime asthma symptom score at or exceeding a prespecified level (e.g., 33 over 7 days; score is defined below) and an average of ≥ 1 puff per day of SABA used for rescue. Patients were then randomized to double-blind inhaled montelukast 1 mg, or matching placebo, using the HandiHalerTM DPI once daily for 2 weeks while continuing open-label mometasone (Period III, treatment 1), all taken in the evening. After a 1-week washout period during which patients continued open-label mometasone plus inhaled placebo (Period IV, washout), patients crossed over to the other double-blind medication (inhaled montelukast or inhaled placebo) for 2 weeks (Period V, treatment 2). SABAs were allowed as needed to treat symptoms, but habitual use was discouraged. An action plan for worsening asthma was provided.

Randomization was determined by a computer-generated allocation sequence generated by the study statistician. Numbered DPI devices and packaging were used to implement allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Spirometry and Efficacy Measurements

All sites utilized a standard spirometer (ndd Medical Technologies, Andover, MA, USA), and procedures conformed to American Thoracic Society standards for acceptability (12). Spirometry was performed between 6 AM and 9 AM after withholding SABAs for at least 6 hours before all study visits. For each measurement of FEV₁ and forced vital capacity, the largest of the three best measurements was recorded.

A daily diary was used to capture symptom scores, SABA use, PEF, and asthma resource utilization.

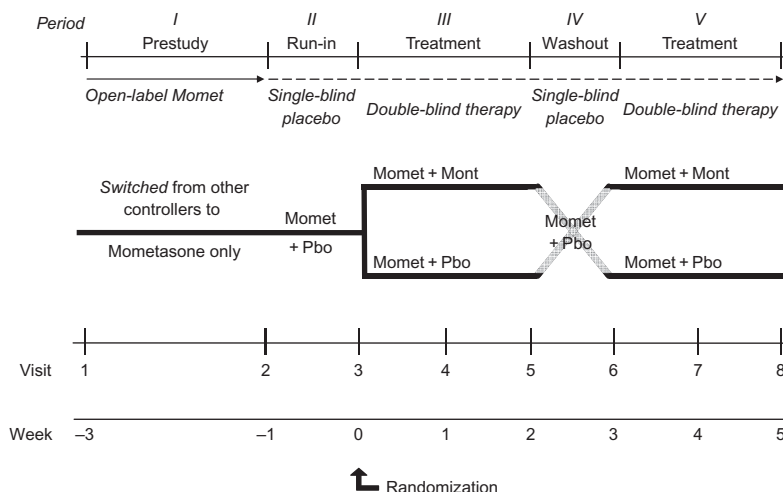


FIGURE 1.—Study design.

Note: Momet, mometasone; Mont, montelukast; Pbo, placebo.

Daytime symptom scores were entered before bedtime and comprised four questions on symptom frequency (“How often did you experience asthma symptoms today?” 0 = “none of the time” to 6 = “all of the time”), bothersomeness (“How much did your asthma symptoms bother you?” 0 = “not bothered at all” to 6 = “severely bothered”), physical activity (“How much activity could you do today?” 0 = “more than usual activity” to 6 = “less than usual activity”), and effect of asthma on activities (“How often did your asthma affect your activities today?” 0 = “none of the time” to 6 = “all of the time”). Nighttime asthma symptoms were entered upon rising in the morning before taking any medications and consisted of a single question regarding nighttime asthma awakenings (“Did you wake up with asthma symptoms?” “no,” “once,” “more than once,” or “awake ‘all night’”). Peak-flow meters were provided (Mini-WrightTM, Alliance Tech Medical, Inc., Granbury, TX, USA) and PEF was performed upon rising in the morning and before going to bed in the evening. SABA use was recorded as the total number of puffs used. Asthma resource utilization was recorded as either “none” or any/all of the following asthma-related resources: unscheduled office visit, emergency room visit, hospitalization, or treatment with steroids.

Efficacy Endpoints

The primary endpoint was the average change from baseline (last pre-randomization value, according to standard statistical principles (13)) in FEV₁ for montelukast plus mometasone versus placebo plus mometasone during the 2 weeks of treatment. The secondary efficacy endpoints were the changes in daytime and nighttime asthma symptom scores. Additional endpoints included as-needed SABA use, AM and PM PEF, the percentage of days with asthma exacerbations, the percentage of days with asthma control, asthma exacerbations, asthma attacks, and total peripheral blood eosinophil counts. The definition of asthma exacerbation in this study generally aligns with the American Thoracic Society/European Respiratory Society definition of “moderate asthma exacerbation”—a day with asthma exacerbation was defined as a day with any of the following: decrease from baseline in AM PEF >20%; AM PEF <180 L/min; increase in SABA use >70% with a minimum increase of ≥2 puffs; increase from baseline in daytime symptom score >50%; nighttime symptom score of “awake all night”; or an asthma attack (14). The definition of asthma attack in this study generally aligns with the ATS/ERS definition of “severe asthma exacerbation”—an asthma attack was defined as symptoms during the previous 24 hours requiring any of the following: systemic corticosteroids; unscheduled visit to the doctor or urgent care clinic; unscheduled visit to the emergency department; or hospitalization (14). A day with asthma control was defined as a day with all of the following: <2 puffs SABA use; no nighttime awakenings; and no asthma attacks.

Safety and Tolerability Endpoints

Safety and tolerability were assessed by clinical review of vital signs, physical examinations, laboratory testing, and adverse experiences (AEs). AEs that were pre-identified to be of potential interest were candidiasis and dysphonia. Also summarized were patients who had any clinical AE, a drug-related clinical AE, a serious clinical AE, and a clinical AE resulting in study discontinuation.

Statistical Methods

The primary hypothesis was that montelukast plus mometasone, compared with placebo plus mometasone, would result in greater improvement from baseline in FEV₁ during the 2 weeks of treatment. The primary hypothesis was tested on the Full Analysis Set population, which included all randomized patients who received at least one dose of study medication and had data at baseline and at least one datapoint on treatment. Patients were analyzed according to the treatment sequence they were randomized to, regardless of the actual treatments they received. The primary endpoint was analyzed based on the data-as-observed approach using weekly changes in a longitudinal data analysis model, which included terms for treatment, time (weeks 1 and 2), treatment-by-time interaction, period, and baseline FEV₁ as a covariate. Given the pharmacodynamic characteristics of montelukast and the 1-week washout period, no carryover effect was assumed. The average change from baseline during the 2 weeks of treatment was tested by constructing the appropriate contrast in the longitudinal data analysis model. Prespecified subgroup analyses for the primary endpoint included age (≤median vs. >median), sex (female, male), race (white, non-white), baseline FEV₁ %-predicted (≤median vs. >median), and BMI (≤25 vs. >25 kg/m² and ≤30 vs. >30 kg/m²). Other continuous endpoints (daytime and nighttime symptom scores, AM and PM PEF, change from baseline in SABA use, percentage of days with asthma control) were evaluated using a methodology similar to that used for the primary endpoint. The percentage of days with asthma exacerbations was based on the completers population using an analysis of variance model with terms for patient, treatment, and period. Peripheral blood eosinophil counts were analyzed using a mixed model with terms for treatment, period, and baseline covariate.

Given the short duration of the treatment periods, the proportion of patients needing systemic corticosteroid rescue, the proportion of patients with asthma attacks, and the proportion of patients with asthma exacerbations were expected to be low. As such, no formal statistical testing between treatments was performed for these three endpoints; summary tabulations and 95% confidence intervals (CIs) for between-treatment differences based on Tango’s method were calculated.

Because all patients were switched to open-label mometasone at the start of the study and may have improved asthma control between visit 1 and randomization, a post hoc analysis of the primary endpoint was performed

in the subset of patients who still met eligibility lung function criteria at the time of randomization (i.e., FEV₁ 50–80%-predicted and FEV₁ increase $\geq 12\%$ between 20 and 30 minutes after SABA administration).

Safety data were analyzed based on the All Patients as Treated population, which included all randomized patients who received at least one dose of study medication. Patients were analyzed according to the treatment they actually received. AEs were assigned to the treatment received at the onset of the AE; AEs occurring during the washout period were counted toward the earlier treatment period. For the prespecified Tier 1 AEs, *p*-values and 95% CIs were to be tested using Tango's method.

Assuming a standard deviation of 0.34 L, a total of 106 patients completing the study would provide 85% power (two-sided at $\alpha = 0.05$) to detect a treatment difference of 0.10 L between inhaled montelukast plus inhaled mometasone versus placebo plus inhaled mometasone in change from baseline in FEV₁. Because there is one primary hypothesis assessed with one variable, and one between-treatment comparison at one timepoint, no multiplicity adjustment for the primary hypothesis was needed. All other endpoints were considered to be supportive or exploratory. Therefore, no adjustment for multiplicity was performed.

RESULTS

Patients

Patient flow through the study is shown in Figure 2. A total of 125 (93.3%) patients completed the study, 130 (97.0%) were included in the primary efficacy analysis, and 130 (94.8%) received treatments in both treatment periods and were included in the safety analysis. Baseline patient characteristics are shown in Table 1. Slightly more than half of the patients were female (51.5%), 46.3% were white, and the mean age was 40.9 years. Half of the patients were receiving ICS at screening. There were no meaningful differences in patient characteristics between the two crossover treatment sequences.

Efficacy

For the primary endpoint of the change from baseline in FEV₁ averaged over the 2-week treatment period, inhaled montelukast plus inhaled mometasone was significantly more effective than placebo plus mometasone (least squares (LS) means 0.22 vs. 0.17 L, respectively; difference = 0.05 L (95% CI: 0.00, 0.09); *p* = .033) (Table 2). There did not appear to be a washout of the montelukast effect during the washout period between the two active treatment periods (Figure 3). Therefore, an analysis based on the first treatment period was performed to corroborate the results from the primary analysis. The LS mean changes in FEV₁ from baseline for montelukast plus mometasone (0.22 L) versus placebo plus mometasone (0.15 L) and treatment difference (0.07 L) were consistent with that observed for the

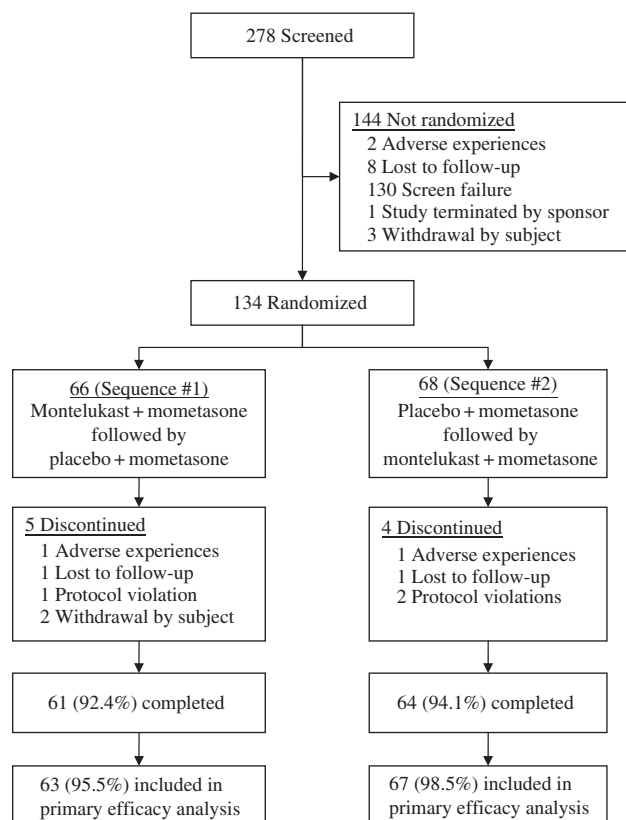


FIGURE 2.—Patient accounting.

TABLE 1.—Baseline patient characteristics.

	Total N = 134
Age (years)	
Mean (SD)	40.9 (15.2)
Range	15.0–74.0
Gender, n (%)	
Male	65 (48.5)
Female	68 (51.5)
Ethnicity ^a , n (%)	
Hispanic or Latino	66 (49.3)
Race ^a , n (%)	
White	62 (46.3)
Black	11 (8.2)
Other	61 (45.5)
Body mass index (kg/m ²), mean (SD)	26.3 (3.9)
Duration of asthma (years), mean (SD)	21.9 (14.2)
Allergic rhinitis, n (%)	78 (58.2)
FEV ₁ (L), mean (SD)	2.16 (0.61)
FEV ₁ (% predicted), mean (SD)	64.54 (11.43)
Prior use of asthma controller medication	
Inhaled corticosteroids	28 (20.9)
Inhaled corticosteroids/long-acting β -agonist combination	39 (29.1)
Montelukast	8 (6.0)

Notes: FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

^aPatient-identified.

TABLE 2.—Primary and key secondary efficacy results.

	N	Baseline/ randomization, mean (SD)	Average change from baseline over 2-week treatment period, ^a LS mean (95% CI)	Treatment difference, LS mean (95% CI)	p-Value
FEV ₁ (L)-primary endpoint					
Montelukast + mometasone	127	2.18(0.60)	0.22(0.15, 0.30)	0.05(0.00, 0.09)	.033
Placebo + mometasone	127	2.19(0.61)	0.17(0.11, 0.23)		
Daytime asthma symptom score					
Montelukast + mometasone	128	2.10(0.85)	−0.39(− 0.49, − 0.29)	−0.15(− 0.26, − 0.05)	.005
Placebo + mometasone	129	2.12(0.85)	−0.24(− 0.35, − 0.12)		
Nighttime asthma symptom score ^b					
Montelukast + mometasone	89	0.70(0.46)	−0.28(− 0.35, − 0.20)	−0.09(− 0.17, − 0.02)	.015
Placebo + mometasone	90	0.71(0.46)	−0.18(− 0.28, − 0.09)		
Total daily SABA use (puffs)					
Montelukast + mometasone	128	3.44(2.21)	−0.87(− 1.21, − 0.53)	−0.60(− 1.26, 0.06)	.073
Placebo + mometasone	128	3.52(2.35)	−0.27(− 0.86, 0.32)		
Days with asthma control (%)					
Montelukast + mometasone	129	NA ^c	35.13(28.52, 41.74)	6.08(1.94, 10.23)	.004
Placebo + mometasone	129	NA ^c	29.04(22.98, 35.11)		
Days with asthma exacerbations (%)					
Montelukast + mometasone	127	NA ^c	9.71(5.51, 13.90)	−5.43(− 8.67, − 2.19)	≤.001
Placebo + mometasone	127	NA ^c	15.14(10.94, 19.33)		
AM PEF (L/min)					
Montelukast + mometasone	127	339.11(93.77)	13.13(7.70, 18.57)	1.51(− 3.22, 6.24)	.529
Placebo + mometasone	128	341.92(98.85)	11.63(5.47, 17.79)		
PM PEF (L/min)					
Montelukast + mometasone	128	345.99(96.64)	9.19(4.04, 14.33)	0.19(− 4.11, 4.49)	.930
Placebo + mometasone	129	348.68(99.48)	9.00(3.32, 14.67)		
Total peripheral blood eosinophils (10 ³ /μL) at week 2					
Montelukast + mometasone	119	0.42(0.36)	−0.05(− 0.09, − 0.01)	−0.07(− 0.12, − 0.01)	.013
Placebo + mometasone	119	0.43(0.36)	0.02(− 0.03, 0.06)		

Notes: ^aAll endpoints measured as the average change from baseline over the 2-week treatment period, except “days with asthma control” and “days with asthma exacerbation,” which were assessed on-treatment only.

^bOnly patients with nighttime symptoms at baseline.

^cThis endpoint was assessed on-treatment only.

CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least squares; NA, not applicable; PEF, peak expiratory flow; SABA, short-acting β-agonist.

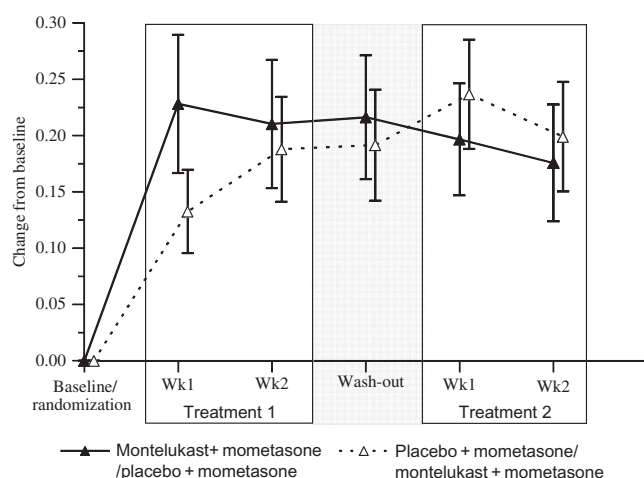


FIGURE 3.—Change from baseline in FEV₁ (L), as mean ± standard error, by treatment sequence and time point.

Note: $p = .033$ for pairwise comparison of montelukast + mometasone versus placebo + mometasone

main results, and a nonsignificant period effect was also confirmed in the primary model ($p = .248$).

In the post hoc analysis of patients who met the screening lung function eligibility criteria not just during the

screening period but also specifically at the randomization visit ($N = 99$ for each treatment), the change in FEV₁ from baseline was significantly greater for montelukast plus mometasone (0.27 L) than for placebo plus mometasone (0.19 L; difference: 0.08 L (0.03, 0.13); $p = .002$).

Prespecified subgroup analyses of the primary showed a noticeable difference favoring montelukast plus mometasone versus placebo plus mometasone for men compared with women, but other differences did not emerge (Figure 4).

Montelukast plus mometasone was significantly more effective than placebo plus mometasone for the change in daytime symptom score ($p = .005$), nighttime symptom score ($p = .015$), percentage of days with asthma exacerbations ($p \leq .001$), percentage of days with asthma control ($p = .004$), and total peripheral blood eosinophils ($p = .013$) (Table 2). There were no significant differences between treatments for AM or PM PEF or total daily SABA use although the latter difference approached significance ($p = .073$).

Exploratory efficacy endpoints that were summarized only (i.e., no formal statistical analysis was prespecified) are shown in Table 3. There were small differences favoring montelukast plus mometasone, although, as anticipated, the number of these events was small.

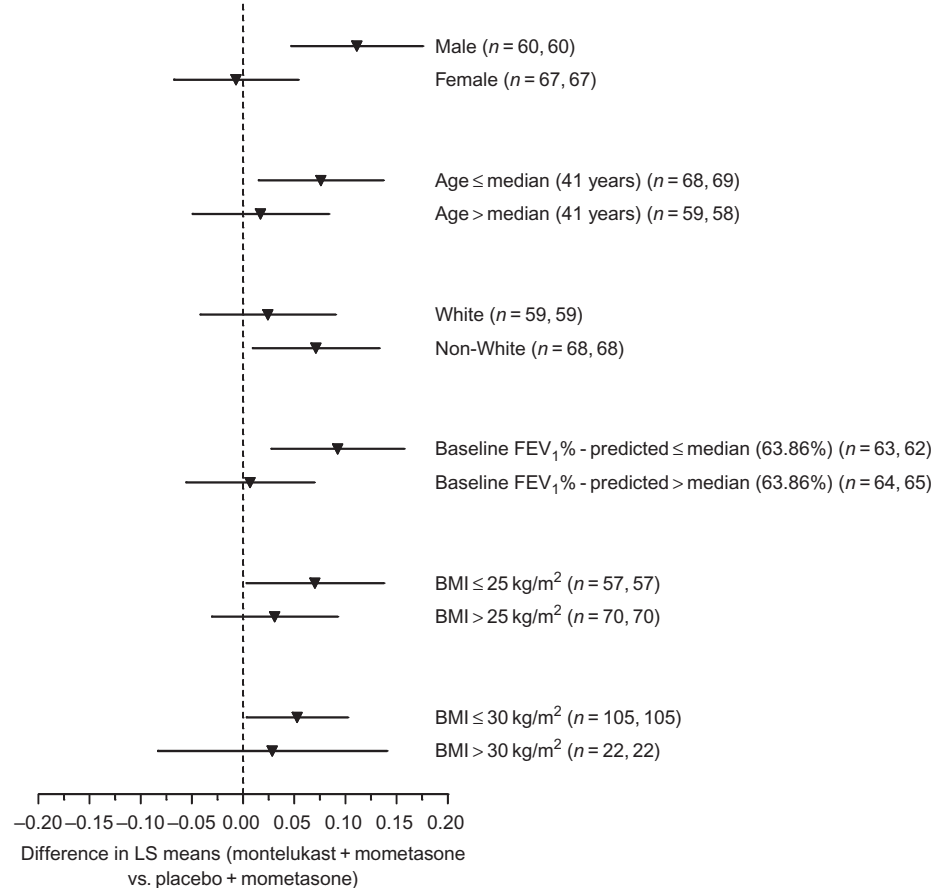


FIGURE 4.—Prespecified subgroup analyses of the primary efficacy endpoint.
Note: $n = x, y$ indicates the number of patients in montelukast+mometasone group (x), number of patients in placebo+mometasone group (y).

TABLE 3.—Summary of other efficacy endpoints.

	<i>N</i>	<i>n</i> (%)	Difference (95% CI)
Patients with asthma attacks			
Montelukast + mometasone	127	6 (4.7)	−0.8 (− 5.8, 4.0)
Placebo + mometasone	127	7 (5.5)	
Patients with asthma exacerbations			
Montelukast + mometasone	127	48 (37.8)	−3.1 (− 12.8, 6.5)
Placebo + mometasone	127	52 (40.9)	
Patients with systemic corticosteroid rescue			
Montelukast + mometasone	127	4 (3.1)	−1.6 (− 6.5, 2.8)
Placebo + mometasone	127	6 (4.7)	

Note: CI, confidence interval.

TABLE 4.—Clinical adverse experience summary.

	Montelukast + mometasone <i>N</i> = 130, <i>n</i> (%)	Placebo + mometasone <i>N</i> = 129, <i>n</i> (%)
Clinical adverse experience	22 (16.9)	23 (17.8)
Drug-related adverse experience ^a	1 (0.8)	0 (0.0)
Serious adverse experience	1 (0.8)	1 (0.8)
Discontinuation due to adverse experience	1 (0.8)	1 (0.8)

Note: ^aDetermined by the investigator to be related to the drug.

Tolerability

Both treatments were generally well tolerated, and there were no meaningful differences between AEs reported when patients were taking montelukast plus mometasone or were taking placebo plus mometasone (Table 4). There was one drug-related clinical AE in a patient taking montelukast plus mometasone (arthralgia), which resolved upon temporarily stopping the study therapy. A total of four serious AEs were reported in three patients; one patient had a head injury that occurred during the open-label run-in period and was

not randomized. Of the two randomized patients with serious AEs, one patient (a 70-year-old male) receiving montelukast plus mometasone experienced two serious AEs, acute pneumonia and acute respiratory failure, but left the hospital against medical advice and subsequently died; one patient receiving placebo plus mometasone experienced asthma. None of the serious AEs was considered by the investigators to be drug-related. No Tier 1 AEs (candidiasis and dysphonia) occurred. The most common clinical AEs were nasopharyngitis (~6.2%)

and asthma (~5.4%). The rates were similar between treatments.

DISCUSSION

The purpose of this proof-of-concept phase IIa study was to evaluate the efficacy of inhaled montelukast plus inhaled mometasone compared with placebo plus inhaled mometasone in patients with chronic asthma. For the primary endpoint of the change from baseline in FEV₁ averaged over the 2-week treatment period, montelukast plus mometasone was significantly more efficacious than placebo plus mometasone. In addition, montelukast plus mometasone was significantly more effective than placebo plus mometasone for the patient-reported endpoints of daytime and nighttime symptoms, and the asthma-control endpoints of days of asthma exacerbation and days with asthma control (during a treatment duration that was only 2 weeks). There was also a significant difference favoring montelukast plus mometasone for blood eosinophil levels, but there were no significant differences between treatments for PEF or SABA use.

We note that the observed treatment difference of 0.05 L was smaller than the anticipated difference of 0.10 L. In the study by Laviolette et al. (2), which served as the basis for the sample size calculation for the present study, the change from baseline in FEV₁ for oral montelukast plus inhaled beclomethasone 200 µg twice daily was 0.14 L over 12 weeks, and the change for beclomethasone alone was -0.02 L. In the present study, these values over 2 weeks were 0.22 L for montelukast plus mometasone and 0.17 L for placebo plus mometasone. When calculated as percent change from baseline, the changes were 5.1% for montelukast plus beclomethasone and 0.7% for beclomethasone alone in the study by Laviolette, and 10.1% for montelukast plus mometasone and 7.8% for placebo plus mometasone in our study. Thus, the smaller-than-expected treatment difference may be related to the relatively large response in the placebo plus mometasone group. This is an intriguing observation given that the total daily delivered ICS dose in the Laviolette study would be considered a medium daily adult dose, compared with a low daily adult dose in our study (10).

The reasons for these findings are unclear and, to the best of our knowledge, no study has ever evaluated oral montelukast added to inhaled mometasone as context for these results. However, several observations may pertain. First, as shown in Figure 3, patients in the first active treatment period had similar responses to treatments, including a very substantial response in the patients receiving placebo. It has been previously shown that steady state with mometasone may not be reached until after 14 days of treatment (15, 16), and that maximal relief may take 1–2 weeks or longer to achieve (17). Thus, it is possible that the effects from mometasone after the 2-week prestudy period had not yet stabilized for

all patients, and improvement may have been continuing for these patients through the placebo run-in period and even into the blinded treatment period. This hypothesis is supported in part by the post hoc analysis of the subgroup of patients who continued to meet the screening criteria for low lung function when measured specifically at the randomization visit; the logic of this subgroup was to exclude patients whose lung function may have improved sufficiently on mometasone that add-on therapy would be less able to show further benefit. This post hoc subgroup showed a larger treatment difference, favoring inhaled montelukast plus mometasone, relative to the full population (0.08 L vs. 0.05 L, respectively).

It is also possible that the lack of washout effect of montelukast between active treatment periods affected the primary endpoint results, resulting in a smaller-than-expected decrease in FEV₁ after patients crossed over to placebo plus mometasone. A related possibility, though somewhat less likely, is that the effect of open-label mometasone was still increasing during the washout period.

Despite the somewhat modest and smaller-than-expected changes in FEV₁, the results for the secondary endpoints were fairly robust, often exceeding those seen in the study by Laviolette et al. (2). Indeed, the montelukast plus mometasone group in our study, compared with the montelukast plus beclomethasone in the Laviolette study had greater improvements in daytime symptoms (-0.39 vs. -0.13, respectively), nighttime symptoms (-0.28 vs. -0.20, respectively), total daily SABA use (approximately -25.3% vs. -5.5%, respectively), percentage of days with asthma exacerbations (9.7% vs. 13.4%, respectively), percentage of patients with asthma attacks (4.7% vs. 6.2%, respectively), as well as change in blood eosinophils (-0.05 vs. approximately 0.01, respectively).

The results of our study are also consistent with and generally supported by the systematic reviews by Joos et al. (7) and Ducharme et al. (8, 9), which found improved efficacy with montelukast and/or other antileukotrienes added to ICS compared with ICS alone, and efficacy comparable to that of doubling the dose of ICS.

A limitation to this study is that, unlike the study by Laviolette et al. (2), there was no placebo-control group or montelukast-only group, which may have helped to better clarify the effect on FEV₁. However, because the purpose of this study was to evaluate the efficacy of adjunctive inhaled montelukast to inhaled mometasone, inclusion of placebo-only or montelukast-only arms would not have provided additional information to address the primary objective. In addition, as noted, it is possible that the initial run-in period and washout period between treatment sequences were not long enough.

CONCLUSIONS

In conclusion, we found that inhaled montelukast plus inhaled mometasone was significantly more effective

than placebo plus inhaled mometasone for the primary endpoint of change from baseline in FEV₁ in patients with chronic asthma. In addition, montelukast plus mometasone was significantly more effective than placebo plus mometasone on several secondary endpoints. Both treatments were well tolerated.

ACKNOWLEDGMENTS

The authors thank Tracey Varnell for her contributions to the conduct of the study and Jennifer Pawlowski for her help with the preparation of the manuscript.

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DECLARATION OF INTEREST

This study was sponsored by Merck & Co., Inc. Drs. Philip and Smugar and Ms. Vandormael are employees of Merck, who may own or hold options to own stock in the company. Dr. Reiss is a former employee of Merck. Dr. Villaran has served as a scientific advisor and has received research support from Merck, GlaxoSmithKline, AstraZeneca, Pfizer, Novartis, and Schering-Plough. Dr. Shah has served as a paid lecturer or served as a scientific advisor or consultant to or received research support from Alcon, AstraZeneca, GlaxoSmithKline, Genentech, Novartis, Meda, Merck, Sepracor, and Teva.

All authors are responsible for the work described in this article, and they contributed to the conception, data interpretation, and drafting of the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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